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Letter to the editor

A novel t(7;13)(p12;q33∼q34) in AML-M2

Chromosomal rearrangements in acute myeloid leukemia (AML) frequently give rise to aberrant transcripts, generating corresponding fusion proteins that are responsible for disease onset (50% of all reported cases) [1,2]. Five percent of such cases harbor rare rearrangements, resulting either in new rare fusion products or in the deregulation/truncation of specific genes [3]. We detected a new t(7;13)(p12;q33∼q34) in an AML-M2 case.

A 26-year-old man was admitted to hospital because of petechiae and a 1-month history of physical weakness. Physical and laboratory examination revealed asthenia, hepatomegaly, anemia, thrombocytopenia, and a white blood cell count of 76×10^9/L, with 70% blasts in the peripheral blood (PB). Cytogenetic analysis showed the karyotype 46,XY,t(7;13)(p11;q34),inv(9)(p11q13)c[30] (Fig. 1Ai). Immunophenotyping on bone marrow cells revealed CD34+, CD13+, CD33+, and CD117+. AML-M2 was diagnosed at that time. Induction and consolidation treatment according to the IDICE LMA99 protocol was administered, resulting in complete remission. Cytogenetic analysis of the PB after remission showed the persistence of the constitutional variant inv(9)(p11q13).

Genomic clones, defining the chromosome 7 and 13 breakpoints (BP), were used for fluorescent in situ hybridization (FISH) analysis, revealing that a more complex rearrangement was present (Fig. 1Aii). The BP on chromosome 7 is located at 7p12, with a 48.4Mb portion between 7p12 and the telomere translocated to the derivative chromosome 13 and a 51.4Mb portion between 7p12 and the centromere retained on the derivative chromosome 7 (Fig. 1, Bi and Bii). The 3Mb portion included between 48.4 and 51.4Mb on the short arm of chromosome 7 was deleted. Similarly, the 101.1Mb portion between the centromere and 13q33~q34 was retained on the derivative chromosome 13, and the 109.5Mb portion between 13q33~q34 and the telomere was translocated to the derivative chromosome 7. Again, the 8.4Mb portion between 101.1 and 109.5Mb on the long arm of chromosome 13 was deleted. More specifically, the chromosome 7 telomeric BP affected the *ABCA13* gene, with the 5' portion retained on the derivative chromosome 13, and the 3' part missing because of the deletion (Fig. 1Bi). On the other side of the deletion, the BP was placed in the proximity of the *COBL* gene, upstream of its first exon (Fig. 1Bii). Likewise, on chromosome 13, the proximal BP affected the terminal portion of the *ITGBL1* gene, leaving its 5' portion on the derivative chromosome 13 and deleting the remaining (Fig. 1Biii), whereas the distal BP mapped downstream to *COL4A1* (Fig. 1Biv). As a result, on the derivative chromosome 7, the rearrangement led to the juxtaposition of two regions of chromosomes 7 and 13, with no specific gene involved, as well as on the derivative chromosome 13 of the *ABCA13* and *ITGBL1* genes. Because of the opposite orientation of the last two genes on the derivative chromosome, no aberrant fusion transcript could be generated (see Fig. 1Aii). We then can conclude that the effects of this rearrangement are the truncation of *ABCA13* and *ITGBL1*, as well as the haploinsufficiency of all the genes included in the chromosome 7− and 13−deleted regions (20 and 30 genes, respectively). These alterations together might coincide with the AML pathogenesis in this case. ABCA13 [4] is a member of the ATP-binding cassette transporter superfamily, whereas ITGBL1 [5] is a protein containing 10 tandem EGF-like repeats, similar to those found in the β-integrin subunits. To our knowledge, no involvement of these two genes with leukemia has ever been described. Our results also provide evidence that complex rearrangements might be hidden in well-defined cytogenetic abnormalities, which a molecular cytogenetic analysis is able to show instead.

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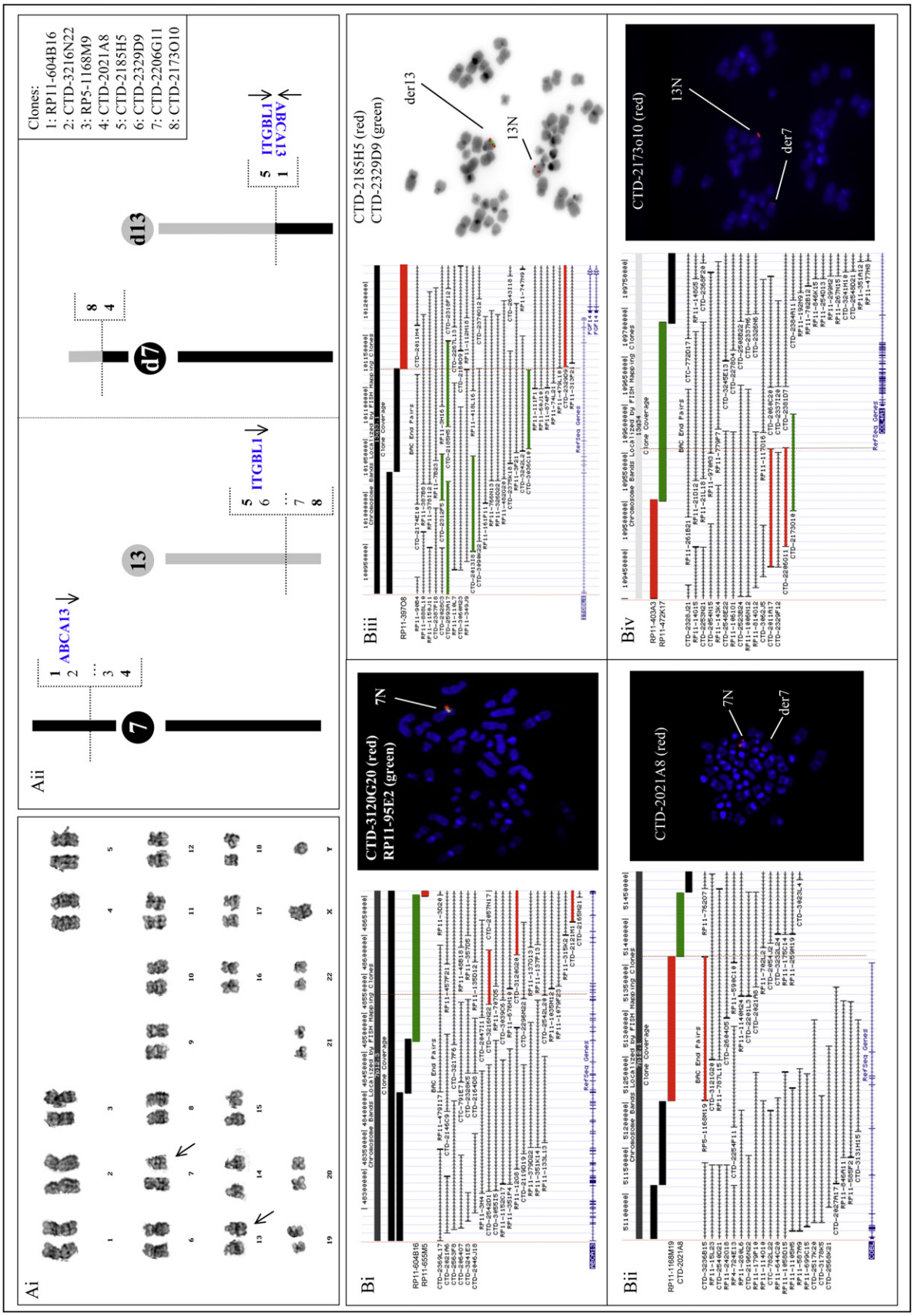
Ai
Aii
Clones:
1: RP11-604B16
2: CTD-3216N22
3: RP5-1168M9
4: CTD-2021A8
5: CTD-2185H5
6: CTD-2329D9
7: CTD-2206G11
8: CTD-2173O10
ABCA13
ITGBL1
Bi
CTD-3120G20 (red)
RP11-95E2 (green)
7N
Biii
CTD-2185H5 (red)
CTD-2329D9 (green)
der13
13N
Bii
CTD-2021A8 (red)
7N
der7
Biv
CTD-2173o10 (red)
13N
der7

Fig 1. (Ai) Patient karyogram. Arrows indicate the derivative chromosomes 7 and 13. (Aii) Schematic representation of the chromosomes involved in the rearrangement (normal chromosomes 7 and 13, and derivative chromosomes 7 and 13). The position of the retained genomic clones (bolded) is indicated both on the normal and on the derivative chromosomes, as well as that of the deleted genomic clones (normal font), which is reported on the normal chromosomes. Vertical black arrows indicate the 5'–3' gene orientation. (B) Physical maps of the four chromosome regions affected by the rearrangement (derived from the University of California–Santa Cruz website, http://www.genome.ucsc.edu/ and adapted), with results from the corresponding fluorescent in situ hybridization (FISH) experiments. FISH was performed as described [6], with genomic clones from either the RPCI (http://www.bacpac.chori.org/) or CALTECH (http://www.tree.caltech.edu/) BAC libraries. Each clone was tested on metaphase spreads from a normal control, confirming its chromosomal location and specificity. Retained clones are indicated in green, and deleted clones appear in red. Genes located in the involved regions are represented as horizontal blue bars. The genomic structure, showing exons as vertical bars, is given. Blue arrows along the genes indicate their 5'→3' orientation. The location of the BP area in each genomic region is indicated by dotted vertical brown lines. Representative results of the FISH experiments are reported on the side of each map. (Bi) The *ABCA13* region at 7p12. FISH results for the CTD-3120G20 and RP11-95E2 clones are shown (the RP11-95E2 BAC clone is located at 50.5 Mb), indicating that both clones are deleted (one signal on the normal chromosome 7 only). Involvement of the *ABCA13* gene was also confirmed by Rapid Amplification of cDNA Ends (RACE)–polymerase chain reaction (PCR) experiments, proving that the BP lies within intron 49. 3'-RACE-PCR experiments were performed with the SMART RACE cDNA Amplification Kit (Clontech, Palo Alto, CA), according to the manufacturer's protocol. Gene-specific primers are available upon request. RACE-PCR products were cloned (Topo-TA cloning kit; Invitrogen, Carlsbad, CA) and sequenced. (Bii) The *COBL* region at 7p12. FISH results for the BAC clone CTD-2021A8 are shown, showing that it is retained on derivative chromosome 7 (one signal on the normal chromosome 7 and one signal on the derivative 7) and positioning the BP upstream to the *COBL* gene. (Biii) The *ITGBL1* region at 13q34. FISH results for the BAC clones CTD-2185H5 and CTD-2329D9 are reported, showing that the first is retained (one signal on the normal chromosome 13 and one signal on the derivative chromosome 13), whereas the second is deleted (one signal on the normal chromosome 13 only). The position of the retained and deleted clones clearly localize the BP within intron 7. (Biv) The *COL4A1* region at 13q33.1. FISH results for CTD-2173O10 are shown, indicating that this clone is translocated (one signal on the normal chromosome 13 and one signal on the derivative chromosome 7), and that the BP is located downstream of the *COL4A1* gene.

Elvira Gerbino[1]
Cinzia Tapinassi[1]
Omar Malazzi
Carla Micucci
European Institute of Oncology
Department of Experimental Oncology
Via Adamello 16, 20139 Milan, Italy

Fondazione Istituto FIRC di Oncologia Molecolare (IFOM)
Via Adamello 16, 20139 Milan, Italy

Maria J. Calasanz
Department of Genetics
University of Navarra
Avda. Pío XII, 55
E-31008, Pamplona, Spain

Jose' M. Beltran-Heredia
Department of Hematology
Hospital de Basurto
Avda. de Montevideo, 18-48013
Bilbao, Spain

Patrizia Gasparini
European Institute of Oncology
Department of Experimental Oncology
Via Adamello 16
20139 Milan, Italy

Fondazione Istituto FIRC di Oncologia Molecolare (IFOM)
Via Adamello 16, 20139 Milan, Italy

Maria D. Odero
Department of Genetics
Division of Oncology Center for Applied Medical Research
University of Navarra
Avda. Pío XII, 55
E-31008, Pamplona, Spain

Pier Giuseppe Pelicci
Elena Belloni*
European Institute of Oncology
Department of Experimental Oncology
Via Adamello 16, 20139 Milan, Italy
Fondazione Istituto FIRC di Oncologia Molecolare (IFOM), Via Adamello 16, 20139 Milan, Italy
*Corresponding author. Tel.: +39-0257489396; fax: +39-0257489851.
E-mail address: elena.belloni@ifom-ieo-campus.it
[1]These authors equally contributed to this work.

References

[1] The Mitelman database of chromosome aberrations in cancer Available at: http://www.cgap.nci.nih.gov/Chromosomes/Mitelman.
[2] Rowley JD. The role of chromosome translocations in leukemogenesis. Semin Hematol 1999;36:59–72.
[3] Giadzik V, Dohner K. Prognostic implications of gene mutations in acute myeloid leukemia with normal cytogenetics. Semin Oncol 2008;35:346–55.
[4] Prades C, Arnould I, Annilo T, Shulenin S, Chen ZQ, Orosco L, Triunfol M, Devaud C, Maintoux-Larois C, Lafargue C, Lemoine C, Denèfle P, Rosier M, Dean M. The human ATP binding cassette gene ABCA13, located on chromosome 7p12.3, encodes a 5058 amino acid protein with an extracellular domain encoded in part by a 4.8-kb conserved exon. Cytogenet Genome Res 2002;98:160–8.
[5] Berg RW, Leung E, Gough S, Morris C, Yao WP, Wang SX, Ni J, Krissansen GW. Cloning and characterization of a novel beta integrin-related cDNA coding for the protein TIED (“ten beta integrin EGF-like repeat domains”) that maps to chromosome band 13q33: a divergent stand-alone integrin stalk structure. Genomics 1999;56:169–78.
[6] Minucci S, Monestiroli S, Giavara S, Ronzoni S, Marchesi F, Insinga A, Diverio D, Gasparini P, Capillo M, Colombo E, Matteucci C, Contegno F, Lo-Coco F, Scanziani E, Gobbi A, Pelicci PG. PML-RAR induces promyelocytic leukemias with high efficiency following retroviral gene transfer into purified murine hematopoietic progenitors. Blood 2000;100:2989–95.